This poster presents nonclinical research conducted to characterize mechanisms underlying findings observed in rat pre- and postnatal development studies for scientific exchange. The data presented do not change the approved indication, contraindications, or prescribing recommendations for oteseconazole. Healthcare professionals should refer to the FDA approved Prescribing Information for complete safety information.

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Correlation of Dietary Antioxidant Levels to Incidence and Severity of Oteseconazole-induced Nuclear Opacities in Peri-Postnatal Development (PPND) Studies

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Background

Oteseconazole (VIVJOA®) is an oral antifungal approved for recurrent vulvovaginal candidiasis (RVVC). In rat PPND studies, nuclear opacities and occasional ocular hemorrhage were reported, leading to its contraindication in females of reproductive potential. These rat ocular findings were highly variable across studies, rat strains, and contract research facilities. Because spontaneous background nuclear cataracts occur in up to 50% of young rats[1], isolating drug related effects requires understanding of the factors that modify baseline risk. The role of oxidative stress in nuclear cataract formation and the protective effects of various antioxidants[2], including vitamin K[3], are well-known.

Methods

Four PPND studies were conducted in pregnant Sprague-Dawley rats (Crl:CD(SD), Hsd(SD), or Crl:WI(Han)) dosed with oteseconazole (7.5 mg/kg/day) from gestation day 6 (GD6) through lactation day 20 (LD20). Ophthalmic evaluations (indirect ophthalmoscopy, slit-lamp biomicroscopy, and/or gross examination) and clinical pathology (hematology, coagulation, serum chemistry) were performed during study. To define windows of lens susceptibility, subsequent PPND studies incorporated cross-fostering designs at two contract research facilities. More recent studies evaluated diets with decreasing antioxidant capacity—PMI 5002 > Teklad 2016C > custom blend—quantified by the ferric reducing antioxidant power (FRAP) assay. Mechanistic investigations included mouse whole-lens explants and mouse and human lens epithelial cells.[4] Oxidative stress was assessed by 4-hydroxynonenal (4-HNE) staining in lenses from rat pups and in vitro lens cells.

Vitamin K and Antioxidant (FRAP) Content in Rat Diets (Study No. 32011898)

Group No.	Diet	Vitamin K1	Vitamin K3	Vitamin K, Total	FRAP [µM Fe^{3+} reduction potential]
1+2	PMI 5002 (High FRAP, Moderate Vit K)	0.448	0.047	0.495	4450
3+6	Teklad 2016C (Low FRAP, High Vit K)	0.061	2.282	2.344	2707
4+5	Custom Blend (Low FRAP, Ultra Low Vit K)	0.138	BQL-<0.009	0.140	1602

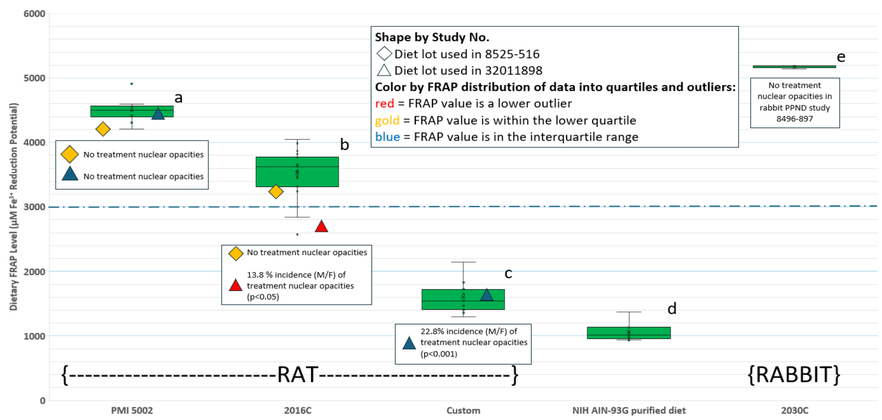
Dietary FRAP values were directly correlated with incidence, laterality, and severity of nuclear opacities (not presented) to identify an antioxidant protection threshold. Human relevance was evaluated using primary human lens epithelial cells, VKOR inhibition assays, human hepatocyte stress-response assays, clinical vitamin K and coagulation biomarkers, and pregnancy outcomes from clinical trials.

Results

- Nuclear opacities were absent in two PPND studies when dietary antioxidant capacity exceeded ~3000 µM FRAP (PMI 5002; some Teklad 2016C lots) but were observed with lower-FRAP diets (Teklad 2016C, custom), reflecting lot-to-lot variability.
- Oxidative injury (4-HNE) localized to anterior lens suture lines adjacent to the fetal nucleus increased with decreasing dietary FRAP, indicating postnatal (lactational) opacity formation.
- Systemic evidence of oxidative stress was observed in rat pups (PND22) and dams (LD20) by elevations in γ–glutamyltranspeptidase that was diet-dependent and correlated with nuclear cataract formation in pups. Rat hepatocytes were ≥2-fold more sensitive to nuclear Nrf2 induction and generation of reactive oxygen species than human hepatocytes (data not shown), reflecting known species differences.[5]

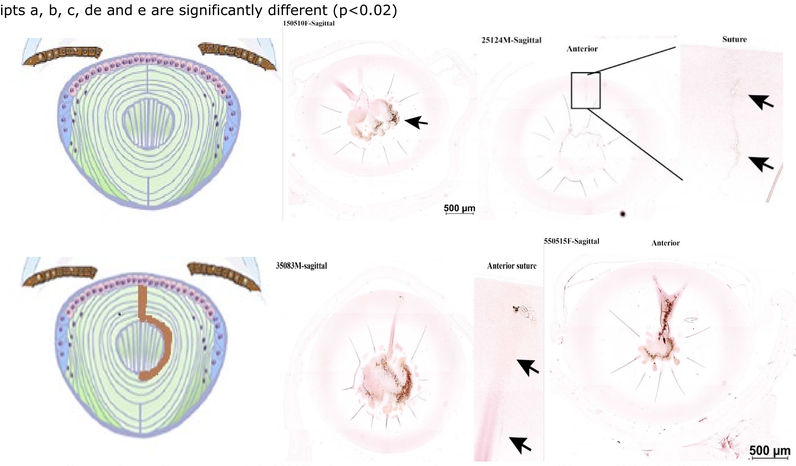
Disclosures: These work were sponsored by Mycovia Pharmaceuticals Inc. (Mycovia), the manufacturer of oteseconazole

Results



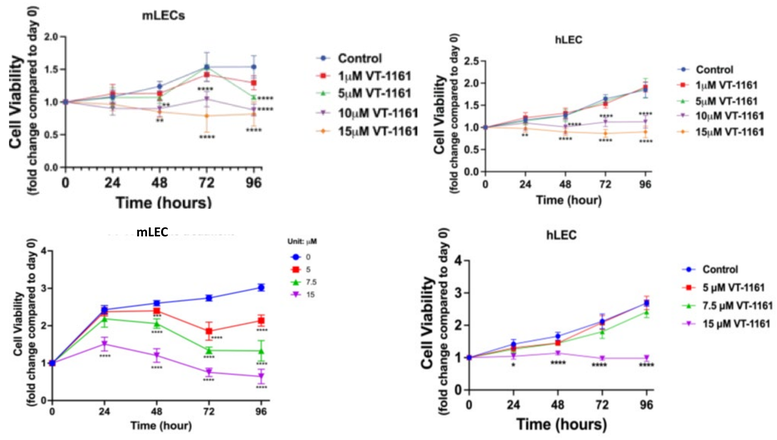
Survey of FRAP Levels Across Commercial Diet Lots and Specific Lots Used in Study Nos. 8525-516 and 32011898.

Superscripts a, b, c, de and e are significantly different (p<0.02)



Localization of Oxidative Damage (4-HNE staining) in Lenses from Study 32011898.

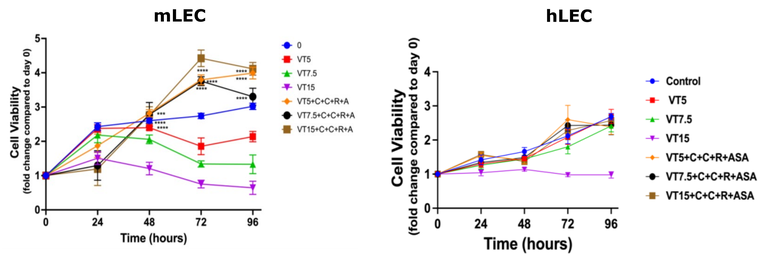
Top left: illustration of embryonic nucleus and fiber cells, Top middle: 4-HNE staining (arrow) in control lens (5002 diet), Top right, 4-HNE suture line staining (insert) from treated lens (5002 diet), Bottom left: colorized schematic to illustrating 4-HNE staining, Bottom middle and right: 4-HNE staining of the Y suture and fiber cells in treated lens (2016C and Custom diet) animals



Effect of VT-1161 (Oteseconazole) on Mouse (mLEC) and Human (hLEC) Lens Epithelial Cell Viability

Results

In vitro, antioxidant combinations protected mouse and human lens epithelial cells from oteseconazole-induced cell death, with minimal toxic concentrations of ~5 µM (mouse) and ~10 µM (human) after 96 hours.



Oteseconazole vs Oteseconazole Plus β-Carotene/ α-carotene/ Retinoic Acid/ Ascorbic Acid (10 µM/1.5 µM/10 µM/0.5 mM) in Mouse and Human Lens Epithelial Cells

β-carotene/α-carotene/retinoic acid/ascorbic acid and N-acetylcysteine/ ascorbic acid (10 mM/3 mM) fully protected mouse and human lens epithelial cells. Protective effects were also observed with antioxidant combinations of lutein/zeaxanthin (10 µM/2 µM) of eicosapentanoic acid/dodosahexanoic acid (50 µM/30 µM).

Conclusions

- Nuclear opacity formation, when observed in rat pups, is driven by dietary antioxidant capacity, not oteseconazole exposure alone.
- A FRAP antioxidant threshold of ~3000 µM Fe^{3+} reduction potential distinguishes diets that prevent vs. allow cataract formation. No opacities were observed in rabbit PPND studies (5200 µM Fe^{3+}). Healthy humans consume ~12 mmol/day.[6] Normal human serum FRAP levels are ~2-3x higher than in rat dams on this study and ~2-3x lower than healthy rats on other diets.
- Final vitamin & FRAP antioxidant content are not quantitated by manufacturers, are subject to lot variability and chow formulation differences between companies (PMI 5002, Teklad 2016C) that negatively influenced the outcome of rat PPND regulatory studies.
- Cataracts arise postnatally due to oxidative injury to anterior lens epithelial cells and suture line disruption.
- Human relevance is low: human LECs are markedly more resistant to oxidative stress, and clinical exposure shows no ocular or coagulation effects (Poster 4332).
- Combined evidence supports a species specific, diet-modulated mechanism and suggest that these rat findings do not translate a risk in humans (Poster 4039).

References

[1]Ban et al., Anim Eye Res. 2008;(29)9-15.
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[4]Fan X, et al. Ophthalmic Research. 2017;(156)103-111.
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[6]Zujko et al., Nutrients 2022; 14(15):3219.

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